201-15144A

HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

Phenol, 2-(1-methylpropyl)-4,6-dinitro-

CAS No. 88-85-7

Submitted to the US EPA

BY

Crompton Corporation.

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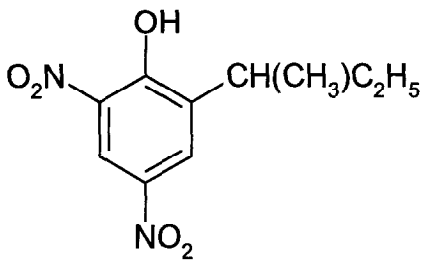
Test Plan for Dinoseb

1. General Information

1.1 CAS Number: 88-85-7

1.2 Molecular Weight: 240.2

1.3 Structure and formula: $C_{10}H_{12}N_2O_5$



1.4 Introduction

Phenol, 2-(1-methylpropyl)-4,6-dinitro- (DNBP) is used as a polymerization inhibitor for the production of styrene. Prior to 1990, DNBP was also used as a pre-emergence herbicide. Based on its toxicity, the use of DNBP as a herbicide is limited to certain government approved agricultural commodities.

2. Review of Existing Data and Development of Test Plan

Crompton Corporation has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for DNBP.

The availability of the data on the specific SIDS endpoints is summarized in Table 1. Table 1 also shows data gaps that will be filled by additional testing.

Table 1: Available adequate data and proposed testing on Phenol, 2-(1-methylpropyl)-4,6-dinitro

CAS No. 88-85-7	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y					Y	N
Boiling Point	Y					Y	N
Vapour Pressure	Y					Y	N
Water Solubility	Y					Y	N
Partition Coefficient (Kow)	Y					Y	N
Environmental Fate							
Biodegradation	Y				Y	N	Y
Hydrolysis	Y			Y		Y	N
Photodegradation	Y				Y	Y	N
Transport and Distribution between Environmental Compartments	Y				Y	Y	N
Ecotoxicology							
Acute Fish	Y	N	N	Y	N	Y	N
Acute Daphnia	Y	N	N	Y	N	Y	N
Acute Algae	Y	N	N	N	N	N	Y
Toxicology							
Acute Oral	Y	Y	N	Y	N	Y	N
Repeat Dose toxicity	Y	N	N	N	N	Y	N
Genetic toxicity – Gene mutation	Y	N				Y	N
Genetic toxicity – Chromosome aberration	N						Y
Reproductive toxicity	Y	N	N	N	N	Y	N
Developmental toxicity/teratogenicity	Y	N	N	Y/N	N	Y	N

A. Evaluation of Existing Physicochemical Data and Proposed Testing

1. Melting Point

The melting point is quoted as 38-42°C in a peer-reviewed publication

2. Boiling Point

The boiling point is quoted as 332°C in EXTOXNET database.

3. Vapor Pressure

Values for vapor pressure quoted in the literature range between 2.3E-5 hPa and 7.0E-5 hPa at 30 – 20°C, respectively.

4. Water Solubility

The water solubility is quoted as 52 mg/L at 25°C in a peer reviewed publication.

5. Partition Coefficient

The Log Pow is quoted as 3.56 in a peer-reviewed publication.

Summary of Physicochemical Properties Testing: Existing data for melting point, boiling point, vapour pressure, partition coefficient and water solubility are considered to fill these endpoints adequately.

B. Evaluation of Existing Environmental Fate Data and Proposed Testing

1. Biodegradation

The biodegradability of the chemical has been estimated using Biowin v4.00 and the results indicate the chemical to not be readily biodegradable. The chemical contains no biodegradable groups, therefore no biodegradation testing is proposed.

A Biodegradation study will be conducted following OECD guidelines.

2. Hydrolysis

A peer-reviewed report in the literature shows DNBP to be stable in aqueous solution over the pH range of 5-9.

3. Photodegradation

The potential for photodegradation of DNBP has been estimated using the AOPWIN v1.90, and indicated atmospheric oxidation via OH radicals reaction with a half-life of 31.8 hours.

4. Transport and Distribution between Environmental Compartments

An Epiwin Level III Fugacity Model calculation has been conducted DNBP and indicates distribution mainly to soil and, to a lesser extent, water for emissions of 1000 kg/hr simultaneously to air water and soil compartments.

Summary of Environmental Fate Testing: Existing data for photodegradation, hydrolysis, biodegradation and transport and distribution between environmental compartments are considered to fill these endpoints adequately.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

1. Acute Toxicity to Fish

   DNBP has been shown to be toxic to fish in several studies reported in the peer-reviewed literature (LC_{50} = 0.08 – 0.7 mg/L).

2. Acute Toxicity to Algae

   DNBP has been shown to be toxic to algae (EC_{50} = 4.3 - > 10 μM) in a study reported in the literature.

   An Acute toxicity to Algae study will be conducted following OECD guidelines.

3. Acute Toxicity to Daphnia

   DNBP has been shown to be toxic to daphnia (EC_{50} = 0.24 mg/L) in a peer-reviewed study reported in the literature.

4. Acute Toxicity to Bacteria (non-SIDS endpoint)

   A value of EC50 > 6.4 mg/L is reported in the literature for this non-SIDS endpoint.

5. Chronic Toxicity to Fish (non-SIDS endpoint)

   The $NOEC_{(weight)}$ for chronic effects on development and growth of fry in this study was < 0.5 μg/L. The concentration not affecting survival of the fry was between 4.9 and 10 μg/L.

Summary of Ecotoxicity Testing: DNBP is toxic to the aquatic environment. All SIDS endpoints have been filled adequately.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

   The acute oral toxicity of a formulation containing DNBP has been examined in two studies conducted to GLP and following EPA OPP guidelines. In these studies the LD_{50} (rat) values ranged from 54.7 to 103.7 mg/kg bw.

2. Acute Inhalation Toxicity (non-SIDS endpoint)

In two GLP studies conducted to EPA OPP guidelines, the acute inhalation toxicity to rats of a formulation containing DNBP was found to be between0.033 and 0.29 mg/L (based on the active).

3. Acute Dermal Toxicity (non-SIDS endpoint)

In two GLP studies conducted using methods similar to EPA OPP guidelines, the acute dermal toxicity to rabbits of a formulation containing DNBP was found to be between 40 and 146 mg/kg bw.

4. Acute I.P. Toxicity (non-SIDS endpoint)

An LD_{50} (mouse) of 14.1 – 20.2 mg/kg is reported in the literature.

3. Eye Irritation (non-SIDS endpoint)

Formulations containing DNBP were highly irritating to the eyes of rabbits in two GLP studies performed to EPA OPP guidelines.

4. Repeat Dose Toxicity

In a combination subchronic feeding and single generation reproduction study, rats were fed DNBP for a total of 153 days at doses up to 500 ppm. The test groups dosed at 300 ppm and higher were terminated at 21 days due to mortality. In the remaining groups, growth was depressed monotonically. Blood alkaline phosphatase, alanine aminotransferase, potassium and BUN were significantly increased, while LDH and cholinesterase were depressed. Residue levels were dose dependent with blood > feces >urine > adipose >brain > liver. Aminopyrine N-demethylase activity was increased. Organ weights were decreased, while the organ weight/body weight ratios increased. A significant pathological change was diffuse tubular atrophy of the testes, particularly at 200 ppm.

Although only an abstract of the study is available in the literature, it is believed there is sufficient detail available to allow an assessment of repeated dose toxicity and no further studies are proposed to fulfil this endpoint.

5. Genotoxicity

DNBP tested negative in a number of Ames tests using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA 100 and Escherichia coli strain WP2 uvrA-, both with and without metabolic activation (Arochlor-induced rat liver S9).

DNBP tested positive in an E. coli polA differential toxicity assay (E. coli strains p3478 & W3110) and in a S. typhimurium differential toxicity assay (S. typhimurium strains

SL4700, SL4525, TA1978 and TA1538), both test conducted without metabolic activation. It also tested positive in a Bacillus subtilis recombination assay (B. subtilis strains M45 & H17) without metabolic activation, but was negative in a yeast gene mutation assay (S. cerevisiae D3) and in a UDS assay (Human Lung Fibroblast cells, strain WI-38) with and without metabolic activation.

In an in vivo Drosophila SLRL test using D. melanogaster, DNBP tested negative when administered to male fruit flies by oral feed.

6. Reproductive and Developmental Toxicity

In a one-generation fertility study DNBP was administered by oral feed to male Sherman rats for up to 77 days. At toxic dose levels the effects upon male reproduction are severe and appear dose related. At toxic dose levels histopathological changes in the gonads are observed that persist following withdrawal of treatment. The extent of the reproductive effects was seen to be beyond what was a consequence of dietary restriction alone. A NOEL of 3.8 mg/kg/day was established for both adult toxicity and reproductive effects, but the extent of the findings suggests that the effects on reproduction are not a consequence of a general systemic toxicity.

There are a number of developmental toxicity studies reported in the literature. In one study, the evaluation of postnatal offspring development following prenatal exposure was examined. Irrespective of the route of administration, the test material was shown to be a developmental toxicant at dose levels that were toxic to the adult. The effects were either embryolethality/embryotoxicity, teratogenicity, fetotoxicity or a combination of effects. The nature of the findings suggest that developmental toxicity was not a consequence of toxicity to the adult. Some species variation in response was observed, but this was influenced by study design. In a study performed on rabbits following EPA guidelines, a NOEL for maternal and developmental toxicity of 1 mg/kg/day was established.

Summary of Human Health Effects Testing: An in vitro chromosome aberration test (OECD 473) will be performed. All other endpoints are considered to have been filled adequately.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance [2] and the systematic approach described by Klimisch et al [3]. These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation [4]. The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing

guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. References

[1] US EPA, EPI Suite Software, 2000

[2] USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

[3] Klimisch, H.-J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25:1-5

[4] USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.